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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,824	09/08/2000	Tongtong Wang	210121.478C11	2868

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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,824	WANG ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,21 and 23* is/are pending in the application.

4a) Of the above claim(s) *1-5,7-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,18,20,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the amendment and 132 Declaration filed June 17, 2003. Claims 1-18, 20, 21 and 23 are pending. Claims 1-5 and 7-17 are withdrawn from consideration as being drawn to a non-elected invention. Applicants arguments and amendments set forth in this response have been fully considered but are nor persuasive to overcome all grounds of rejection. It is noted that the following grounds of rejection have been modified in view of the 132 Declaration filed June 17, 2003. This action is made final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 18, 20, 21 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting the presence of lung adenocarcinoma in a human patient by detecting the presence of a polypeptide encoded by SEQ ID NO: 808 in a lung cancer cell or by detecting an increase in the level of said polypeptide in a lung cancer cell relative to the level of polypeptide in a normal cell, does not reasonably provide enablement for methods which detect the presence of lung cancer in any patient using a binding agent that binds to a polypeptide having at least 90% identity with a polypeptide encoded by SEQ ID NO: 808. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for detecting the presence of cancer wherein said methods comprise contacting a sample with an agent that binds to a polypeptide encoded by SEQ ID NO: 808 or a sequence having 90% identity thereto, detecting any peptide that binds to said agent, comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of cancer in a patient. The specification teaches a cDNA for a clone "L552S" wherein the cDNA has the sequence of SEQ ID NO: 808. The specification also teaches a polypeptide encoded by said cDNA wherein said polypeptide has the sequence of SEQ ID NO: 809. In particular, the specification (pages 159-160) teaches that the cDNA of SEQ ID NO: 808 was isolated from a lung adenocarcinoma cDNA library and subtracted against a pool of normal human cDNA libraries of lung, liver, pancreas, skin, kidney, brain and resting PBMC. The specification does not provide any information on the level of expression of the polypeptide encoded by SEQ ID NO: 808 in lung cancer cells versus normal cells. However, in the response filed June 17, 2003, Applicants filed a 132

Declaration establishing that the L552S protein is expressed in lung adenocarcinoma cells and is not expressed in normal lung cells. The Declaration does not state the source of the lung cancer and normal lung cells, but based on the teachings in the specification it has been interpreted that the cells analyzed were obtained from humans. If this interpretation is not correct, Applicants are requested to please clarify the record. Accordingly, Applicants have enabled methods for detecting the presence of lung adenocarcinoma in a human patient by detecting the presence of a polypeptide encoded by SEQ ID NO: 808 in a lung cancer cell or by detecting an increase in the level of said polypeptide in a lung cancer cell relative to the level of polypeptide in a normal cell.

However, the specification has not established that any protein containing a fragment of SEQ ID NO: 809 will be correlated with the occurrence of cancer. It is noted that the claims as written define the agent that is used to detect a polypeptide, but the claims do not specifically define the polypeptide. Accordingly, the claims include detecting variants and fragments of the polypeptide of SEQ ID NO: 808. No information is provided on any subfragments of the polypeptide encoded by SEQ ID NO: 808 which are unique to cancer cells and would be expected to be present in other proteins that are associated with the occurrence of cancer. No guidance is provided in the specification as to which subfragments of the protein encoded by SEQ ID NO: 808 would be expected to be present in other proteins and which would be useful for diagnosing cancer. It would require undue experimentation to practice the claimed invention because this would necessitate screening the human genome and the

genomes of other organisms for the presence of nucleic acids encoding 10 mer fragments of the polypeptide encoded by SEQ ID NO: 808, isolating the larger length or full length molecules, and assaying such molecules to determine whether they encode for proteins which are specifically expressed in cancer cells and not expressed in normal cells. The specification does not provide any information regarding the length, structure or functional activity of the larger or full-length polynucleotide or the peptide encoded thereby. Additionally, the claims as amended include detecting polypeptides having 90% identity with the polypeptide encoded by SEQ ID NO: 808. However, the specification has not taught any variants of the polypeptide encoded by SEQ ID NO: 808 which would be associated with cancer. No guidance has been provided as to how to modify SEQ ID NO: 808 at specific positions so as to generate additional nucleic acids encoding for proteins that are correlated with cancer. It is highly unpredictable as to how modification of the polypeptide encoded by the polynucleotide of SEQ ID NO: 808 would alter the functional activity of the polypeptide and would affect its association with the occurrence of cancer. Additionally, the specification has shown only that the cDNA of SEQ ID NO: 808 is expressed in human lung adenocarcinomas. The specification has not established that this cDNA is expressed in other types of cancer or in cancers from non-humans. Lastly, the specification (page 65) teaches that "lung tumor proteins" are expressed at a level of at least a 2 fold increase in tumor cells versus normal cells. However, the specification does not define what constitutes a "predetermined cut-off value" and it is unclear as to what quantity of a polypeptide of SEQ ID NO: 809 or subfragments or variants having 90% identity thereof would be

required to be indicative of cancer. Case law has established that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement" (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001). In the instant case, the specification has not fulfilled this requirement because the specification has not adequately taught one of skill in the art how to detect the presence of cancer in a patient using an agent that binds to a polypeptide encoded by SEQ ID NO: 808, a polypeptide by a polynucleotide having 90% with SEQ ID NO: 808 or a polypeptide comprising a fragment of a polypeptide encoded by a polynucleotide having the sequence of SEQ ID NO: 808.

RESPONSE TO ARGUMENTS:

In the response filed June 17, 2003, with respect to the grounds of rejection over the detection of fragments of the L552S polypeptide, Applicants state that the claims have been amended. However, it is noted that the claims do not specifically define the actual polypeptide that is detected as indicative of lung cancer, but rather define only the agent that is used to detect the polypeptide. The agent binds to "a polypeptide encoded by the polynucleotide of SEQ ID NO: 808" or to "a polypeptide comprising an amino acid sequence having at least 90% identity to the amino acid sequence of a polypeptide encoded by the polynucleotide sequence of SEQ ID NO: 808." The claims do not recite any particular level of specificity of the agent and do not require that the detected polypeptide is of any particular length or sequence. Accordingly, the claims include detecting fragments and variants of the L552S polypeptide. However, the

specification has not taught an association between lung cancer and any peptide fragments or variants of L552S.

Applicants state that "the skilled artisan would immediately recognize that such variants would very likely also be overexpressed in lung cancer, since they would be expressed from the same gene and their expression would be regulated by the same regulatory control elements as L552S polynucleotides of SEQ ID NO: 808." This argument is not persuasive because even if the variants were synthesized from the same gene, there is no evidence that these uncharacterized variants would also be expressed at increased levels in lung tumor cells. Splicing is a mechanism by which cells control the expression levels of nucleic acids and there is no evidence of record to show that any potential splice variants of SEQ ID NO: 808 are expressed at the same levels in lung cancer cells. Furthermore, proteins having amino acid substitutions often display significantly different expression patterns and stability, making it unpredictable as to whether a variant of L552S would be over-expressed in and associated with lung cancer. Furthermore, the claims include detecting variants derived from different genes than 808 because the claims include detecting polypeptides from any patient. However, the specification has not established that a homolog of L552S exists in non-humans and is associated with the occurrence of lung cancer.

Lastly, applicants assert that determining a cut-off value is routine and that the disclosure provides sufficient guidance for selecting a cut off value. It is stated that requiring an absolute cut-off value is scientifically inappropriate. This argument is not persuasive because the specification as originally filed does not set forth what is

considered to constitute a cut-off value. It is unclear if the cut-off value is obtained from a normal lung cell or from some other undefined source. The claims do not require detecting an increase in L552S polypeptide as compared to a normal cell. Rather, the claims broadly recite comparing the amount of polypeptide to a predetermined cut-off value and from this comparison determining the presence of a lung cancer. It is noted that the rejection does not in any way require that the claims recite an "absolute cut-off value". Rather, the rejection is based on the breadth of the claims as written and the fact that the specification as originally filed did not clearly set forth what is intended to be encompassed by the concept of a pre-determined cut-off value. There is no guidance for how one uses the information obtained by comparing the amount of a polypeptide to an undefined/uncharacterized cut-off value in order to determine the presence of a lung cancer in a patient.

3. Claims 6, 18, 20, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for detecting the presence of cancer wherein said methods comprise contacting a sample with an agent that binds to a polypeptide encoded by SEQ ID NO: 808 or a sequence having 90% identity thereto, detecting any peptide that binds to said agent, comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of cancer in a patient. While isolated polypeptides consisting of SEQ ID NO: 809 and isolated

polypeptides encoded by SEQ ID NO: 808 meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the claimed genus of any polypeptide that binds to a binding agent which binds to a polypepide encoded by SEQ ID NO: 808 or to a polypeptide encoded by a polynucleotide having 90% identity with a polynucleotide of SEQ ID NO: 808 . *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Accordingly, knowledge of the sequence of fragments encoded by SEQ ID NO: 808 does not allow the skilled artisan to envision all of the contemplated larger and full-length polypeptides

encompassed by the claims. The claims require detecting proteins that have been defined with respect to the fact that they bind to a binding agent that binds to an unspecified degree to a polypeptide encoded by SEQ ID NO: 808 or to polypeptides having 90% identity to a polypeptide encoded by SEQ ID NO: 808. The specification does not sufficiently describe these proteins in terms of their structural properties (length, identity of flanking amino acid sequences, etc) or functional properties (e.g., activity of the encoded peptide). The specification does not teaches only the polypeptide of SEQ ID NO: 809 and does not teach any other polypeptides comprising fragments of SEQ ID NO: 809. Additionally, the claims include detecting allelic variants of the polypeptide encoded by SEQ ID NO: 808. However, the specification does not adequately describe the structural and functional properties of any polypeptide encoded by a polynucleotide having 75% identity with SEQ ID NO: 808. Accordingly, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the polypeptides required to practice the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

RESPONSE TO ARGUMENTS:

In the response of June 17, 2003, Applicants assert that they have disclosed a representative number of species within the claimed genus. However, Applicants have disclosed only 1 species within the much broader genus of variants, homologs and

fragments of L552S. Again, it is noted that the claims do not directly define the protein that is detected as indicative of lung cancer. Rather, the claims indirectly define the protein in terms of the agent that binds thereto. The specificity of binding is not stated, nor are the lengths and specific sequence of the protein defined. The claims include the detection of polypeptides that can be bound by an agent that binds to a polypeptide that is encoded by SEQ ID NO: 808 or a polypeptide having 90% identity with a polypeptide encoded by SEQ ID NO: 808. Accordingly, the disclosure of one member of this genus does not constitute a "representative number." Furthermore, providing one sequence does not provide and show possession of all variants and homologs and fragments of that sequence. Applicants assert that the instant application "satisfies both the possession and notice functions of the written description requirements." However, the claims do not recite any functional attributes for the detected polypeptide. Rather, again, the claims define only the structure of the polypeptide and this structure is defined indirectly in terms of what binding agent binds to the polypeptide. Applicants assert that by providing a full length polypeptide encoded by SEQ ID NO: 808, Applicants have also disclosed all fragments of SEQ ID NO: 808. While it may be possible to write down all possible fragments of L552S that could exist, this is not equivalent to being in possession of the specific polypeptide fragments of L552S that exist in nature and which could be used for the diagnosis of lung cancer.

Claim Rejections - 35 USC § 112

4. Claims 6, 18, 20, 21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 18, 20, 21 and 23 are indefinite over the recitation of "predetermined cut-off value." The specification does not provide a clear definition for what is intended to be encompassed by this phrase and there is no art recognized definition for this phrase. Accordingly, one cannot determine what is intended to be encompassed by a predetermined cut-off value.

RESPONSE TO ARGUMENTS:

In the response filed June 17, 2003, Applicants state that the meaning of the phrase "predetermined cut-off value" is well understood and that the specification provides two examples of determining a cut-off value. However, providing examples of what might be included by the phrase does not provide a complete definition of the phrase. The specification does not provide a definition as to what the full scope of this phrase is intended to include and thereby one cannot determine the meets and bounds of the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
September 4, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER